UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,594	05/03/2002	Dan L. Eaton	10466/360	2707

9157 7590 06/30/2006

GENENTECH, INC.
1 DNA WAY
SOUTH SAN FRANCISCO, CA 94080

EXAMINER	
WEGERT, SANDRA L	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/30/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,594	EATON ET AL.	
	Examiner	Art Unit	
	Sandra Wegert	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-8 and 11-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-8 and 11-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/7/06,4/3/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, and/or Claims

A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. This application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid.

The Response, Information Disclosure Statement, and Amendments, submitted 3 April 2006, have been entered. Claims 1-5, 9 and 10 are canceled. The Information Disclosure Statement submitted 7 March 2006, has been entered.

Claims 6-8 and 11-17 are under examination in the Instant Application.

The text of those sections of Title 35, U.S. Code, not included in this action can be found in a prior Office action.

Maintained/New Objections and/or Rejections

35 U.S.C. § 101/112, first paragraph-, Lack of Utility, Enablement.

Claims 6-8 and 11-17 are rejected under 35 U.S.C. 101, as lacking utility. The reasons for this rejection under *35 U.S.C. § 101* are set forth at pages 4-10 of the previous Office Action (4 January 2006). Claims 6-8 and 11-17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial

asserted utility or a well established utility for the reasons set forth in the previous Office Action (4 January 2006), one skilled in the art clearly would not know how to use the claimed invention.

Applicants argue (*Remarks*, 3 April 2006, page 6 and throughout) that the data presented in the instant Specification are enabling for the polypeptide of SEQ ID NO: 88. They argue that the PRO1270 nucleic acid is a diagnostic marker for *normal lung*, and point to the results of the assay which showed transcription of the PRO1270 DNA in one normal versus cancerous tissue. Applicants point out that the PRO1270 data of Example 18 refers to pooled transcription data (Response, page 9 and throughout).

Applicant's arguments (3 April 2006) have been fully considered but are not found to be persuasive for the following reasons:

In the instant case, the specification provides data showing an indeterminate increase in mRNA in one normal tissue (see Example 18, Specification). However, there is no evidence regarding whether or not PRO1270 polypeptide levels are also increased in *normal lung* tissue versus *lung* tumor. Furthermore, as discussed in the previous Office Action (3 April 2006, pages 4 and 5), what is often seen is a *lack* of correlation between mRNA levels and increased peptide levels (Pennica, et al, 1998, Proc. Natl. Acad. Sci., 95: 14717-14722). As discussed by Haynes et al (1998, Electrophoresis, 19: 1862-1871), polypeptide levels cannot be accurately predicted from mRNA levels, and that, according to the results presented, the ratio varies from zero to 50-fold (page 1863). The literature cautions researchers against drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, Hu et al. (2003, Journal of Proteome Research 2: 405-412) analyzed 2286 genes that showed a greater than 1-fold difference in mean expression level between breast cancer samples and normal

samples in a microarray (p. 408, middle of right column). Hu et al. discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section).

Applicants also discuss Nelson v Bowler (206 USPQ 881, 1980) as support for the contention that their invention has a substantial utility (page 7, 3 April 2006). However, the case of Nelson v Bowler only contemplates the degree of certainty required of experimental evidence submitted in support of a contended utility and that, furthermore, the data need not point to treatment of human diseases. The Court ruled that a showing of practical utility for a composition may be satisfied by an adequate showing of any pharmacological activity, without a showing of direct therapeutic utility. Thus, the identification of some specific pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and thus satisfies the utility requirement. See MPEP 2107 (III). The conclusions are that an invention need not have a therapeutic value, and the applicant need not prove that the utility is true "beyond a reasonable doubt." As discussed above, the instant specification does not suggest a specific function for the claimed polypeptide- indeed the disclosed polynucleotide and claimed polypeptide were not specifically identified at filing- so the believability of submitted evidence is not a critical issue in patentability of the claimed polynucleotide.

As the Utility Guidelines (Federal Register, 2001, 66: 1092-1099) say in the discussion of *Fujikawa v Wattanasin,* "where a class of proteins is defined by common structural features, but

evidence shows that the members of the class do not share a specific, substantial functional attribute or utility, despite having structural features in common, membership in the class may not impute a specific or substantial utility to a new member of the class. When there is a reason to doubt the functional protein assignment, the utility examination may turn to whether or not the asserted protein encoded by a claimed nucleic acid has a well- established use. If there is a well-established utility for the claimed protein and the encoding nucleic acid, the claims would meet the requirements for utility under 35 U.S.C. 101. If not, the burden shifts to the applicant to provide evidence supporting a well-established utility. *There is no per se rule regarding homology, and each application must be judged on its own merits."* (Italics added).

Given the small increase in transcription of PRO1270 DNA, and the evidence provided by the current literature, it is clear that one skilled in the art would not assume that a small decrease in message would correlate with significantly decreased polypeptide levels. Further research needs to be done to determine whether the small decrease in PRO1270 message supports a role for the peptide in detecting or treating cancerous tissue; such a role has not been suggested by the instant disclosure. The requirement for further research makes it clear that the asserted utility is not yet in currently available form, i.e., it is not substantial. This further experimentation is part of the act of invention and until it has been undertaken, Applicant's claimed invention is incomplete. As discussed in Brenner v. Manson, (1966, 383 U.S. 519, 148 USPQ 689), the court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and,

> "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Accordingly, the Specification's assertions that the claimed PRO1270 peptide has utility in the fields of cancer diagnostics and cancer therapeutics are not substantial.

There is no evidentiary support that PRO1270 is involved in the etiology of cancer in the one sample disclosed in the instant Application. Furthermore, as noted above, the decrease in PRO1270 message, and in only one tissue, points away from its role in a disease. At any rate, one result is too little data to make a conclusion about PRO1270 and cancer. It should be noted that the *specific* function of the PRO1270 polypeptide has not been disclosed by Applicants or by recent research. Although transductional and structural information are not absolutely necessary when applying for a patent on a new protein, it would be very useful to have such information for the PRO1270 polypeptide, since there is only one positive data point in the transcription assay, and that is in one normal tissue. Finally, it is noted that the literature cautions researchers from drawing conclusions based on small changes in expression levels between normal and cancerous tissue. See Hu et al. (2003, Journal of Proteome Research 2:405-412) as discussed above.

Applicants discuss (Response, 3 April 2006, page 9 and throughout) points from case law in reference to the utility rejection, most of which the examiner agrees with. However, the fact patterns of the cases cited have little connection with utility/enablement as applied to the instant Application. Whatever the asserted specific utility might be - diagnosis of cancer, for example- it is **not** "more likely than not" or true "to a reasonable probability" (Fujikawa v. Wattanasin, 1996, 93 F3d 1559, 39 USPQ2d 1895) since the increase in message was found in only one

normal tissue sample.

Applicants assert that references submitted by the PTO do not support the contention that protein and mRNA are, at best, weakly correlated (Remarks, page 14). Applicant's arguments have been fully considered but are not found to be persuasive. Haynes et al. clearly state "[p]rotein expression levels are not predictable from the mRNA expression levels" (pg 1863, top of left column) and "only the direct analysis of mature protein products can reveal their correct identities, their relevant state of modification and/or association and their amounts" (pg 1870, under concluding remarks). Feroze-Merzoug et al. (Cancer and Metastasis Rev 20: 165-171, 2001) even disclose that "[t]he lack of correlation between mRNA and corresponding protein is evident even in low eukaryotic cells such as yeast. Therefore, it will be necessary to profile both mRNA and protein for a complete picture of how cells are altered during malignant transformation" (pg 168, col 1). Clearly, Haynes et al. and Feroze-Merzoug et al. indicate that mRNA levels do not predict protein levels.

Applicants discuss the Declarations submitted previously under 35 USC §1.132 to explain how data were gathered, etc. For example, the Declaration from Dr. Grimaldi explains that data from several of the same tissues are pooled. This results in a difference of expression between the positive and negative tissue of 2-fold.

Applicant's arguments (3 April 2006) have been fully considered but are not found to be persuasive for the following reasons:

As discussed in the previous Office Action (4 January 2006), a 2-fold increase is not large and may be less likely to indicate disease (Hu, et al, 2003, Journal of Proteome Research 2:405-412), or may be sufficient (Applicant's Response, page 14). However, the type or

magnitude of increase is not at issue in this case. All that is known about the PRO1270 peptide is that it is increased in one normal tissue sample. It cannot be determined what the function of the protein is in that tissue; certainly the tissue provides no clues. It is hard to conceive of a specific and substantial utility for a protein for which so little data or information is given. For example, why were other tissues not tested, as was the case for other PRO polypeptides?

Applicants do not know the function of the PRO1270 polypeptide. For this reason, detecting the PRO1270 mRNA or polypeptide has no specific function, since it is not useful to detect a protein for which a function has not yet been identified, and additionally might only be underexpressed in one cancer. Since the asserted utility for the PRO1270 polypeptide is not in currently available form, the asserted utility is not substantial.

35 USC § 112, first paragraph – Written Description.

Claims 14 and 15 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. The reasons for this rejection under 35 U.S.C. § 112, first paragraph, are set forth at pp. 10-11 of the previous Office Action (4 January 2006). Briefly, the Applicants were not in possession of all or a significant number of polypeptides that have 95-99% homology to SEQ ID NO: 88, while retaining the function of SEQ ID NO: 88.

Applicants discuss the legal standards applied when evaluating Written Description,

including the requirement that written description depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure (pages 24-28, 3 April 2006). The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case. However, Applicants have not described or shown possession of all polypeptides 95-99% homologous to SEQ ID NO: 88, *that are functionally equivalent to SEQ ID NO: 88*. Nor have Applicants described a representative number of species that have 95-99% homology to SEQ ID NO: 88, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 88. Applicants screened for one PRO1270 sequence, and used that one sequence in expression protocols (see Example 130 and Table 8). There is no discussion in the instant disclosure about the structure of PRO1270, nor about related molecules, such that molecules that vary as much as 5% from PRO1270 could be evaluated for similarity of function. There is no discussion about the art-recognized molecules to which PRO1270 might be related. Indeed, the PRO1270 protein has not been identified. Applicants produced PRO1270 recombinantly; therefore, there is no information about the molecule that might come from certain more-complicated isolation techniques (such as, for example, protein folding characteristics and charge). Applicants have not made sequences different from SEQ ID NO: 87 or 88 and have provided no information about related molecules.

Applicants discuss the legal standards applied when evaluating Written Description, stating that sufficiency of support under Written Description depends on "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter" (page 20, 28 September 2005), and cite relevant case law (In re Kaslow 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir.

1983). However, In re Kaslow discussed the *timing* of the disclosure in a way sufficient to show that the applicant was in possession of the claimed invention. The examiner takes no issue with the discussion of general requirements for evaluating Written Description in this case or with the fact that Applicants are indeed in possession of SEQ ID NO: 88 in this Application. However, Applicants have not described or shown possession of all polypeptides 95-99% homologous to SEQ ID NO: 88, *that are functionally equivalent to SEQ ID NO: 88*. Nor have Applicants described a representative number of species that have 95-99% homology to SEQ ID NO: 88, such that it is clear that they were in possession of a genus of polypeptides functionally similar to SEQ ID NO: 88.

Applicants also discuss the legal standards applied when evaluating Written Description, (page 28, 3 April 2006) implying that there is adequate written description of what is claimed in the instant application. They cite Appellants arguments and the CAFC's initial comments from a case recently before the Federal Circuit (*In re Wallach*, 378 F3d 1330, 71 USPQ2d 1939 (Fed. Cir. 2004)). The examiner agrees that, if one full polypeptide is disclosed in an application, the applicant presenting that peptide is in possession of all possible DNA's encoding that peptide. However, In re Wallach presented very different data. They had disclosed only a partial sequence of a polypeptide and were then making a claim to all the nucleic acids that encoded the *full-length* polypeptide. Furthermore, the Federal Circuit answered this question in the **negative**. The court ruled that the written description requirement for claims to the DNA molecules was **not** satisfied by disclosure of a partial amino acid sequence of the encoded protein. Given the very different fact patterns and that the case cited was answered in the negative, In re Wallach does not appear to support the Applicant's arguments.

As discussed in the previous Office Action (8 April 2004) even a very skilled artisan could not envision the detailed chemical structure of all or a significant number of encompassed PRO1270 polypeptides, and therefore, would not know how to make or use them. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of making. The claimed product *itself* is required. Recitation of the phrase "in lung tissue samples..." is not adequate to describe the PRO1270 polypeptides that have 95-99% homology to the PRO1270 polypeptide, since there was no reduction to practice to support the amended claims. Applicants made no variant polypeptides, and as recited in the current Written Description Guidelines, Applicants must have invented the subject matter that is claimed and must be in "possession" of the claimed genus (Federal Register, 2001, Vol. 66, No. 4, pages 1099-1111, esp. page 1104, 3rd column).

Conclusion

No claims are allowed.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sandra Wegert whose telephone number is (571) 272-0895. The examiner can normally be reached Monday - Friday from 9:00 AM to 5:00 PM (Eastern Time). If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Brenda Brumback, can be reached at (571) 272-0961.

The fax number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the

Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SLW
21 June 2006

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud